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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/866,233	5/7/97	LEE S	241800

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EXAMINER	
ALLEN, M	
ART UNIT	**PAPER NUMBER**
1645	46

DATE MAILED: 02/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/966,223	Applicant(s) Lee
	Examiner Marianne P. Allen	Group Art Unit 1645

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *3, 11-15, and 24-31* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *3, 11-15, and 24-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

Examination of this application is resumed following suspension at the request of applicant in order to submit declaration evidence.

Claims 3, 11-15, and 24-31 are under consideration by the examiner.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant points to basis for the claimed subject matter on pages 9-10 of the specification. The specification at these pages does not appear to disclose the hybridization conditions recited in the claim with respect to Figures 11A and 11B. Only Figure 2 is mentioned. Applicant is requested to point to specific basis (page and line number) for the claim limitations. Should this rejection be overcome, this claim would be subject to the enablement rejection set forth below.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 3 is directed to nucleic acids encoding hamster GDF-1. It is noted that this claim is not properly dependent upon claim 22 (see below). The specification provides the sequences of mouse and human GDF-1. The specification further indicates that they have less conservation across species (69%) than other members of the TGF-β superfamily. (See page 31.) The specification contains no disclosure of the expected structure for other members of this family or what structural features identify a protein as a GDF-1 protein. Furthermore, as the activity of GDF-1 was not known at the time of the invention, the specification does not enable any assays for identification of GDF-1.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the mouse and human sequences, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides (which would be required for recombinant production of the protein) and proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of

isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

See also the July 22, 1997, CAFC decision of The Regents of the University of California v. Eli Lilly and Company where generic claims to vertebrate and mammalian insulin cDNA's were found to be invalid because of lack of adequate written description where only the rat sequence was disclosed.

Again, although the specification discloses the human and mouse GDF-1 sequences, the specification fails to define the structural features that characterize GDF-1 that would permit one of ordinary skill in the art to recognize the structure of hamster GDF-1.

Claims 3, 11-15, and 24-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to nucleic acid sequences, vectors, host cells, and methods of producing the encoded protein. The specification fails to enable how to use these inventions without requiring undue experimentation as set forth in the prior Office actions. The stated uses of these inventions require knowledge of the biological activity of the encoded protein.

Biological properties are alleged based upon the similarity of the GDF-1 amino acid sequence to the TGF-β family. However, there is no evidence of record that GDF-1 is a biologically useful protein possessing any particular properties. (See specification page 12, lines 8-20.) The similarities between GDF-1 and the TGF-β family members range from 26-52% on the amino acid level and these proteins are not deemed to be predictive of the biological properties possessed by GDF-1. The biological activities of the TGF-β family are diverse and it could not have been predicted which activity GDF-1 would have, if any. As such, the specification does not enable using the GDF-1 protein as disclosed in the specification. For example, there is no disclosure of any disease state that can be treated with this protein nor any tumors, genetic diseases, or developmental anomalies that has been associated with this gene or protein. It would require undue experimentation to practice any of these uses. The examiner is unaware of any tumors, genetic diseases, or developmental anomalies that have been associated with this gene or protein even now, well after the effective filing date.

In rebuttal of this position and to establish a biological activity for GDF-1, applicant has submitted the Ebendal declaration under 37 CFR 1.132. This declaration sets forth that recombinant human GDF-1 (amino acids 255-373 fused to 34 additional amino acids) was produced in E. coli and recovered as a dimer. This product potentiates human NT-3 fibre outgrowth. The assays used to establish this biological activity are referenced to Ebendal (1995) and Ernfors (1990). The declaration asserts that this biological activity on neurons is similar to other members of the TGF-β superfamily.

First of all, the particular material tested is not disclosed in the specification. That is, while Figure 11B discloses the human GDF-1 sequence, the portion of this protein and the particular fusion partner used in the declaration experiments do not appear to be disclosed in the specification. Use of the particular pRSET vector by Invitrogen does not appear to be disclosed in the specification. Use of a dimer versus a monomer does not appear to be disclosed in the specification. The fibre outgrowth assay of Ebendal et al. (1995) was developed after the effective filing date of the application. The Ernfors et al. (1990) reference is also post-filing date for the ultimate parent application. Furthermore, it discloses fibre outgrowth activity of NT-3 (although not named as such in this reference) but does not disclose similar activity of TGF-β superfamily members or GDF-1 proteins. It is noted that the declaration evidence indicates that GDF-1 alone was ineffective to evoke fibre outgrowth.

It appears that the potentiating activity between the TGF-β superfamily member OP-1 and NT-3 was not known until well after the effective filing date. (See Bengtsson et al., Journal of

Neuroscience Research, 1998.) It is noted that the receptors discussed were not known at the time of the invention nor does the reference generally postulate this activity to all other members of the superfamily. The involvement of the GDF family was only determined well after the effective filing date. (See Ebendal et al., Journal of Neuroscience Research, 1998.) It was not discovered until well after the effective filing date that TGF-β3 potentiates the survival achieved with NT-3 and NT-4. (See Krieglstein et al., Neurochemical Research, 1996.)

Massague provides a review of the TGF-β superfamily at approximately the time of the invention. The reference sets forth the diverse effects of the various members of the superfamily. The potentiating effect of the Ebendal declaration is not disclosed.

For all of these reasons, the Ebendal declaration is not sufficient to overcome the enablement rejection.

As set forth in the prior Office action, the specification has not informed those skilled in the art how to use the claimed invention. Nothing in the specification as filed would lead one of ordinary skill in the art to evaluating this activity nor associating it with a particular member of the TGF-β superfamily or NT-3. Clearly, the experimentation involved to reach such a discovery was extensive and not routine. Applicant is reminded that the specification is required to clearly state how the claimed invention is to be used. It should be apparent to one of ordinary skill in the art how the claimed invention is to be used after reading the specification. One of ordinary skill in the art should not have to envision, infer, or "dream up" potential uses or perform

experimentation requiring such ingenuity, decision-making, and judgment to determine how to use the claimed invention.

Claims 3 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites "hamster." However, none of the sequences set forth in claim 22 upon which it depends are hamster sequences. As such, this claim is not properly dependent and confusing.

Claim 26 does not indicate any operable linkage between the DNA and the vector as appears to have been intended.

Applicant's arguments in the preliminary response filed 11/17/97 are not persuasive. Hoban et al. establishes that it was only well after the effective filing date of the invention that the biological activities of this protein were being discovered and assays being developed. There is no statement of use for the protein in the specification as a factor to stimulate immediate early gene expression in neural cell lines. Nothing in the specification would lead one of ordinary skill in the art to this use.

Applicant's specification is an invitation to experiment to determine how to use GDF-1. This specification is analogous to that in Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001,

1005, which was not deemed to be enabling. "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research." The specification speculates on possible activities of GDF-1. None of the particular activities disclosed for other TGF-β superfamily members have been shown for this protein. None of the uses set forth in the specification could be practiced at the time of the invention without undue experimentation. Providing a laundry list of potential uses, some of which are diametrically opposed to each other, is not deemed to be enabling.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Friday from 9:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703) 308-3995. Official FAX communications may be directed to either (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
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